Remarks

This Amendment is in response to the Office Action dated **May 28, 2008.**

Claims 32, 34 and 36 are pending in the application. Facts and explanations are presented below that show patentability of the claimed subject matter.

I. Claim Rejections -35 USC§ 112(1st Paragraph)

Claims 32, 34 and 36 have been rejected under 35 U. S .C. § 112, first paragraph, declaring that they introduce new matter and fail to comply with the written description requirement. The rejection is traversed.

In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* (identical language) support for the claimed subject matter at issue. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996); *In re Wright,* 9 USPQ2d 1649, 1651 (Fed. Cir. 1989). The test for sufficiency of support is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Company v. Far-Mar-Co., Inc.*, 227 USPQ 177 (Fed. Cir. 1985)

In making the claim rejections under 35 U.S.C. § 112, first paragraph, the Examiner states that the specification and the originally filed claims do not support the claim limitations. Specifically, it is stated that the originally filed application does not mention induction of differentiation of epidermal cells in lesional skin and the regression and/or disappearance of said skin lesions in relation to the applied dosages and amounts of cyclopamine. It is stated that nowhere in the originally filed application a general teaching is found that cyclopamine is to be administered in a sufficient amount that induces differentiation of epidermal cells in lesional skin and the regression and/or disappearance of said skin lesions in a psoriatic patient.

Applicant disagrees and points out to the following.

"Summary Of The Invention" on page 4 of the specification states directly and unambiguously that the described *"cyclopamine induced clearance of psoriatic lesions from the* *skin of patients is associated with the causation of cellular differentiation in lesional epidermis"* (see lines 14-18). Thus, a person of ordinary skill in the art reading the originally filed application learns and understands clearly that the clearance of psoriatic lesions in response to the described treatment is associated with induction of differentiation of the epidermal cells in lesional skin.

The originally filed application indicates further that the optimal amount of cyclopamine in a pharmaceutical form and optimal dosing for a patient depend on factors well known in the art and can be determined by published methods of optimization (see page 15, line 25 to page 16, line 1). Besides the particular examples presented, the specification points out also to the sparing of the undifferentiated cells in the non-lesional epidermis and hair follicles following exposure to the same dose of medicament causing clearance of skin lesions and indicates that this facilitates administration also by other modes of administration and provides information about the suitable doses with other pharmaceutical forms (see e.g. page 16, lines 16-23). A skilled artisan routinely adjusts the doses of prior art medicaments to be administered to a patient according to the technical effects and therapeutic results to be caused. Once informed about the expected effect and results of an administration of a medicament, the skilled artisan can readily optimize the dosage for a patient.

In the present case, the skilled artisan has no uncertainity concerning the effect and therapeutic results to be produced by the administration of a sufficient amount of cyclopamine to a psoriasis patient.

The specification teaches cyclopamine-induced clearance of psoriatic skin lesions in association with induction of differentiation of the epidermal cells in lesional skin and describes that this is a dose dependent outcome. For example, administration of cyclopamine for a day only is described to have caused on average a slower pace of decrease in the severity scores of lesions in comparison to the continuous administration of cyclopamine for 3 to 4 days. It is described further that administration of cyclopamine for a day, unlike the situation with the 3 to 4 fold greater dosage, also failed to cause clearance of the lesions in about one third of cases (see page 26, line 26 to page 27, line 12 and see Table I). Still further, it is stated that administration of cyclopamine for a day not only failed to cause clearance of the lesions in about one third of cases but the severity scores of lesions even started to *increase* upon discontinuation of the administration of medicament (see page 27, lines 8-12). Thus, the skilled artisan understands clearly that whereas administration of a sufficient dose of cyclopamine can cause clearance of the psoriatic lesions, a suboptimal dose fails to provide clearance.

The skilled artisan sees further from the specification that the normalization of psoriatic lesional skin by administration of cyclopamine is dose dependent and that a suboptimal dose that is effective to inhibit proliferation of the epidermal cells in lesional skin is ineffective to cause normalization of lesional skin. Design of the investigations where cyclopamine cream is applied onto only half of a psoriatic plaque followed by the excision and analyses of entire plaque provides an objective means of assessment of the effects of varying cyclopamine doses in the same plaque and patient. This is because the cyclopamine cream diffuses from the directly applied half to the adjacent half and the cells therein receive relatively lower doses of cyclopamine in comparison to the cells in the half of lesion onto which the cyclopamine cream is applied directly.

Example of such a testing described in the specification shows in this respect that the half of lesion receiving a relatively lower dose of cyclopamine exhibited inhibition of proliferation of the epidermal cells but morphological normalization of epidermis in association with the induction of differentiation of epidermal cells failed to materialize (see page 20, line 27 to page 21, line 5 and Figures 2I, 2J and 2K). Figure 2I shows a section from the half of lesion onto which cyclopamine was applied directly and Figure 2K shows a lower magnification view of the same half together with the adjacent non-lesional skin. The epidermis in the lesion half onto which cyclopamine was applied directly is seen to be indistinguishable from the non-lesional skin in terms of frequency and position of the proliferating cells, in terms of the re-appearance of granular cells and in terms of morphology. Figure 2J shows a section from the junctional area of the two halves of the lesion and shows inhibition of proliferation in the epidermis adjacent to the half of the lesion onto which cyclopamine was applied directly. However, it is seen that the epidermis wherein proliferation was inhibited failed to normalize morphologically (Figure 2J; notice that the dermis below has also not normalized). Thus, the skilled artisan sees for himself/herself that a suboptimal dose of cyclopamine effective to inhibit proliferation of the epidermal cells in psoriatic lesional skin is ineffective for normalization of lesional skin.

The skilled artisan knows that without morphological normalization of the psoriatic lesional skin, it is impossible to speak about the clearance or disappearance of a lesion in a patient and he/she sees from the specification that said therapeutic outcome requires administration of a dose surpassing a dose sufficing to inhibit proliferation of epidermal cells in lesional skin. Other investigations with varying doses of cyclopamine concur and show that a suboptimal dose fails to produce clearance of the lesions and the severity scores of lesions start to worsen upon discontinuation of administration of medicament (see page 26, line 26 to page 27, line 12). The skilled artisan learns in addition that the cyclopamine-induced clearance of psoriatic lesions is associated with induction of differentiation of the epidermal cells in lesional skin (page 4, lines 14-18). He/she sees further that an indicator of the causation of differentiation of the epidermal cells in lesional skin and regarded to be one of the first signs of effective treatment of psoriasis is also described to accompany the cyclopamine-induced therapeutic outcome (see page 28, line 20 to page 29, line 9).

At least for the aforementioned reasons, claims 32 and 34 have written description support in the originally filed application and they do not introduce new matter.

With respect to claim 36, the specification provides explicit written description support on page 23, lines 18-20 for the limitation relating to the time period and the data in Table I show that the treatments with cyclopamine on average caused greater than 80% decrease in the severity scores of lesions by 4 days (i.e. within the recited time period). The skilled person clearly learns that the treatment results can be quantified in the manner claimed, and produces the claimed result. Thus the specification "reasonably conveys to the artisan that the inventor had possession at that time of the subject matter" of claim 36. The applicant has provided a written description of the subject matter recited in claim 36. No treatment was known in prior art that could provide such an expeditious therapeutic result.

II. Claim Rejections 35 USC § 103

Claims 32, 34 and 36 have been rejected for being obvious in view of *Beachy et al* (US Patent No. 6,432,070). The rejection is traversed.

Beachy et al disclose on the one hand an unlimited number of compounds that are said to inhibit Hedgehog (Hh) signaling (see column 19, line 22 to column 29, line 32; column 50, line 23 to column 67, line 32) and disclose on the other hand a long open-ended list of disorders (including those that are poorly defined or undefined; see e.g. column 8, lines 34-49) that are said to be treated by administration of a subject compound (see column 7, line 49 to column 8, line 67; column 29, line 33 to column 43, line 56). However, there is not a description of a single instance of a treatment of an enlisted disorder. In such a situation where there are endless possibilities of "treatment" but no description of an actual treatment of an enlisted disorder, it is impossible to state that a therapeutic outcome in a particular disorder is made anticipated or obvious by the disclosure.

Since *Beachy et al* do not describe a treatment of an enlisted disorder, it has to be looked if they describe technical effects caused by use of a Hh antagonist and if so, whether or not the described effects make the subject matter of any of the claims 32, 34, 36 obvious.

Disclosures of *Beachy et al* have been analyzed in previous submissions in this application (see e.g. the 2/14/2007 dated Amendment and Appendix A) and in the parallel application (see the 6/11/2007 and 2/20/2009 dated Amendments filed in the US patent application No. 10/682584). Reference is made to said analyses to avoid unnecessary repetition. Suffice it to point out that the teachings in *Beachy et al* are inoperative in entire categories of its disclosure and, therefore, the skilled artisan has to carry out an undue amount of experimentation just to distinguish an operative teaching of *Beachy et al* from an inoperative one (see the above mentioned submissions for examples). In addition the unsupported disclosures of *Beachy et al*, particularly concerning the effect of a subject Hh antagonist on the differentiation of cells are typically ambiguously worded (e.g. "affection", "alteration", "change", "control", "management", "manipulation", "modulation', "regulation" of differentiation) and also self-contradicting even for a particular cell type (see the aforementioned submissions and see further below).

It is clear that, in the absence of evidence or actual results, mere naming of various possible effects of a method of treatment *so as to include explicitly the opposite effects in a patent disclosure and to contend that the disclosure anticipates or makes obvious, regardless of which effect is obtained,* is baseless.

A skilled artisan presented with the *Beachy et al* publication would take it into account as a whole and look for support for a disclosure in the document itself and/or in the rest of art. In this respect, the exemplification and other experimental findings described in *Beachy et al* teach that treatment with a Hh antagonist will cause *inhibition of differentiation* and inhibition of proliferation of the treated cells. In the exemplification of invention, *Beachy et al* describe and conclude that *sufficiently high doses of cyclopamine consistently and selectively inhibited the differentiation events induced by Hh signaling* (column 58, lines 15-19; column 63, lines 24-29; column 5, lines 26-29; column 6, lines 46-49). See column 3, lines 9-12 and lines 39-42 for descriptions of inhibition of differentiation of various other cell types as well in response to inhibition of Hh signaling. The *Ericson J et al Cell* 1995*;* 81:747-756 publication cited in column 3, lines 26-27 also describes causation of an inhibition of differentiation effect when the cells are treated with a specific inhibitor of Hh signaling. Said publication describes induction of the same differentiation events by Hh signaling as described by *Beachy et al's* exemplification and describes inhibition of the same differentiation events by treatment with a specific inhibitor of Hh signaling.

The treatment outcomes contemplated on the basis of described experimental findings with epithelial cells are again causation of the inhibition of differentiation and inhibition of proliferation of the treated cells. See column 39, line 65 to column 40, line 12 describing that Hh signaling induces differentiation and proliferation of various epithelial cells and "thus" the subject method can be used in treatment of the proliferative disorders involving said cells (see column 35, lines 46- 59 for a similar contemplation with another epithelial cell type).

Specifically with epidermal cells (the epithelial cells covering body surface), *Beachy et al* have no description of an actual treatment with a Hh antagonist. They mention, on the other hand, contemplation of the treatment of epidermal cells with a Hh antagonist to cause inhibition of proliferation, as quoted also in the Office Communication. Whereas the subject method using a Hh antagonist is consistently stated by *Beachy et al* to cause inhibition of proliferation of the epidermal cells, the skilled artisan sees that the statements concerning the effect on their differentiation are self-contradicting. Thus, besides the statements quoted in the Office Communication, *Beachy* et al refer in column 38, line 61 to column 39, line 15 to paraoral ulcers (ulcers of the skin around mouth) and teach that treatment with a Hh antagonist can be used to inhibit proliferation and to inhibit differentiation of the epithelial cells to obtain a beneficial therapeutic result. In the immediately following sentence, the same method of treatment is said to be beneficial in treatment of the wounds resulting from psoriasis (column 39, lines 16-19).

The Examiner argues that state of the art at the time of the filing of present application was such that *induction* of differentiation of the epidermal cells in lesional skin would reasonably be expected to naturally occur when cyclopamine is administered in an effective amount to a patient having psoriasis. This argument runs contrary to the facts. The only description of an administration of an effective amount of cyclopamine found in *Beachy et al* speaks about causation of an *inhibition of differentiation* effect on the treated cells (see column 58, lines 15-19; column 5, lines 26-29; column 6, lines 46-49). Further; as indicated also *by Beachy et al* (column 29, lines 39- 45), Hh signaling had been found in prior art to be broadly utilized in induction of differentiation of *various* cell types, including the epidermal cells (see below) and therefore the naturally expected effect of a treatment with a Hh antagonist *was* an inhibition of differentiation effect. Causation of an inhibition of differentiation effect by an effective amount of a Hh antagonist is "a change in the…state of differentiation of a cell" but it is a change separate and distinct from the presently described induction of differentiation effect. The presently described effect is highly unexpected in view of the descriptions in prior art.

The Examiner refers to the statement in column 29, lines 45-47 in *Beachy et al* to argue further that the presently described induction of differentiation of epidermal cells by use of cyclopamine was made obvious by *Beachy et al.* For several reasons, said statement does not make the presently claimed invention obvious. *Beachy et al* mention in the immediately preceding sentence that Hh signaling is broadly employed in the formation of differentiated tissues in vertebrates (column 29, lines 39-45). Furthermore, considering the hundreds of cell types and tissues known in vertebrates, the statement quoted by the Examiner does not make it obvious at all as to which of the precisely opposite effects mentioned by *Beachy et al* will obtain for a particular cell or tissue let alone under what conditions.

The presently claimed invention is not made obvious by the unsupported and self-contradicting disclosures in the *Beachy et al* publication wherein there is not a single instance of a description of a treatment of an enlisted disorder. To the contrary, the presently claimed invention is highly unexpected and nonobvious not only in view of *Beachy et al* as a whole but also the entire prior art as shown below by multiple findings of fact.

(i) Causation of inhibition of proliferation of cells does not make their differentiation expected or anticipated. It is well known in art that cellular proliferation can be inhibited without induction of differentiation.

(ii) With regard to the administration of cyclopamine to a patient having psoriasis, the investigation results described in the instant application show that a dose of cyclopamine effective to inhibit proliferation of the epidermal cells in lesional skin does not produce morphological normalization of the lesional skin and does not produce clearance or disappearance of lesions unless a much greater dose is administered (see Section I above). It is also common knowledge in art that a potent inhibitor of proliferation used in treatment of psoriasis (methotrexate) does not provide the presently described therapeutic results; clearance of lesions by said treatment is considered an unrealistic expectation and typically several weeks to months of treatment is required for objective improvement and regression (see the review articles cited on page 3, lines 11-14 of specification).

(iii) Hh signaling was described in prior art to have a direct stimulatory effect on cellular proliferation *(Barnes E et al, EMBO Journal* 2001;20:2214-2223). Causation of an inhibition of proliferation effect on the cells was therefore a naturally expected outcome of the application of a Hh antagonist to cells. The therapeutic effect expected to be achieved by administration of a Hh antagonist to a patient was similarly an inhibition of proliferation. The effect that a skilled artisan can unambiguously derive from *Beachy et al* is also an inhibition of proliferation effect upon treatment with a Hh antagonist. *Beachy et al* commonly refer to the treatment of a "proliferative' or "hyperproliferative" disorder by administration of a Hh antagonist. They describe experimental findings showing stimulation of proliferation of various epithelial cells by Hh signaling and also the inhibition of proliferation of said cells by administration of a Hh antagonist and state that *"therefore"* or *"thus"* the subject method can be used for treatment of proliferative or hyperproliferative disorders involving epithelia (see column 35, lines 46-59; column 39, line 65 to column 40, line 12; see column 41, lines 31-35 for a similar contemplation in psoriasis).

Adjustment of the dose of a medicament according to the expected effects in a patient is a routine practice in art. Starting at a dose below that of a dose expected to produce a known effect, gradually increasing until the expected effect is observed and stopping administration at the minimum dose effective in producing the expected effect was something the skilled artisan already well versed. *Beachy et al* also teach the skilled artisan to do so (column 44, lines 14-24). Thus, by common knowledge and by the explicit teaching of *Beachy et al*, the skilled artisan administering a Hh antagonist to a patient would be careful not to exceed a minimal dose effective in producing the expected effect. The only therapeutic effect that a skilled artisan can unambiguously derive from *Beachy et al* is the causation of an inhibition of proliferation effect on the cells treated with a Hh antagonist. The effects recited in the instant claims 32 and 34 were totally unknown and unexpected in prior art. Furthermore, the presently described clearance or disappearance of psoriatic lesions was widely considered in prior art an unexpected outcome and the patients and their physicians were advised to be realistic in their expectations (see e.g. the review article cited on page 30, lines 24-25). Accordingly the presently claimed invention is highly unexpected and nonobvious in view of prior art besides not being inherently present in prior art.

(iv) Hh signaling was known in prior art to be required for normal functioning of various cell types in an adult, in particular, stem cells were described to have an absolute dependence on Hh signaling *(Zhang Y et al, Nature* 2001;410:599-604). A skilled artisan was further aware that adverse effects of prior art psoriasis medicaments on stem cells and on other undifferentiated cells severely limit the doses that can be administered to a patient (see e.g. the review article cited on page 3, lines 8-9 of specification). The skilled artisan would therefore be discouraged by the actual experimental findings in prior art and warned about administering a Hh antagonist to a psoriasis patient. If he/she would at all be motivated by *Beachy et al* to administer a Hh antagonist to a psoriasis patient, he/she would certainly aim not to exceed a minimal dose that would be effective to produce the effect expected in prior art. The effect and therapeutic outcome recited in the instant claims 32 and 34 were unknown in prior art and would not be obtained by a skilled artisan following the teachings of *Beachy et al.*

It is clear that the sparing of the undifferentiated cells in the basal layer of epidermis and in hair follicles (well known sites of stem cells and progenitor cells) in the non-lesional skin receiving the same dose of cyclopamine as the disappeared lesions was also highly unexpected and surprising in view of prior art.

(v) Lesional skin in psoriasis contains numerous other cell types besides the epidermal cells. It is unknown a *priori* that the effects of a Hh antagonist on the different cell types in a tissue will be in the same direction or therapeutically beneficial. For example, a recently issued US patent filed before the priority date of present application describes the effects of Hh proteins (and agonists thereof) on lymphocytes and, on the basis of said effects, teaches to administer a Hh *agonist* (i.e.. an *upregulator rather than inhibitor* of Hh signaling) for treatment of psoriasis (see the US patent 6951839, column 7, lines 29-37). Further, the patentee of US 6951839 was specifically aware of the related US patent applications of *Beachy* (see column 46, lines 30-36). Still further, the proprietor of US 6951839 is the same as that of US 6291516 which has largely overlapping disclosure with that of *Beachy et al* and has word-by-word identical teachings with *Beachy et al* specifically concerning psoriasis. The application for US 6951839 was filed after the application for US 6291516. Evidently, it was not obvious or convincing to the same proprietor that psoriasis could be treated beneficially by an antiproliferative embodiment of the subject method using a Hh antagonist.

(vi) Hh family of proteins were discovered originally for their effects on embryonal patterning where they acted to induce differentiation of various cell types. Thus, the expected effect of treating cells with a Hh antagonist was the causation of an inhibition of differentiation .This expectation was borne out in numerous investigations in prior art. *Beachy et al* cite some of these publications and describe similar results in the exemplification. Specifically concerning differentiation of the epidermal cells, the entire prior art was again teaching away from the presently claimed invention.

See *Stone DM et al, Nature* 1996;384:129-134 teaching that *"Hh system may provide differentiative signals to basal cells in the skin throughout life"* (page 133, left column, 2nd paragraph under Discussion).

See *Maesawa C et al, Genes Chromosomes Cancer* 1998;21:276-279 for a similar teaching and see *Struhl G et al, Development* 1997;124:2143-2154 describing that Hh signaling specify cuticular structures that differentiate from the epidermal precursor cells.

See *Nilsson M et al, Proc Natl Acad Sci USA* 2000;97:3438-3443 teaching that GLI-l executes Hh signaling in the cell nucleus and that it induces proliferation as well as differentiation of the Hh target cells in skin (page 3442, left column, 4th paragraph).

See *Oro AE et al, Science* 1997;276:817-821 which is cited by *Beachy et al* and incorporated by reference (see column 64, line 50 and column 68, lines 56-57) describing consequences of upregulation of Hh signaling in skin. *Oro AE et al* describe that upregulation of Hh signaling caused hyperproliferation in the interfollicular epidermis and that the epidermal cells therein differentiated normally (page 818, left column, last sentence and page 820, Fig. 3).

(vii) The specification in the present application describes downregulation of the epidermal growth factor receptor (EGFR) expression by administration of a specific inhibitor of Hh signaling to the lesional skin where EGFR expression was markedly increased. In association with the cyclopamine-induced differentiation of epidermal cells in lesional skin, expression of EGFR is shown to be rapidly normalized (page 13, line 19 to page 20, line 2; page 28, line 20 to page 29, line 9; Figures 4J,4K, 4L). No such treatment of a human patient or description existed in prior art. However, this is a surprising and unexpected result in view of the prior art which had described that it is rather the Hh signaling itself that causes downregulation of EGFR expression in the epidermal cells or surface epithelium in another species *(Mohler J et al, Development* 2000;127:55-63).

(viii) A prior art publication co-authored by the first-named inventor of US 6432970 and submitted and published after the filing of the application for US 6432970 describes experiments where cells were treated with cyclopamine or with a derivative thereof to inhibit their proliferation *(Taipale J et al, Nature* 2000;406:1005-1009). Treatments with varying doses of cyclopamine or a derivative thereof causing maximal inhibition of proliferation in association with abolishment of Hh signaling are described (see page 1007, Figure 3; notice in Figure 3c and in Figure 3d plateau in the effect of inhibitor at the highest doses). The authors do not describe an induction of differentiation effect on the treated cells.

(ix) Psoriasis was considered in prior art to be a primarily T-cell mediated disease caused by CD4(+) and CD8(+) T lymphocytes. Many treatments directed specifically to said cells were described in prior art but none was found to have a therapeutic efficacy that can even be compared to that described in the present application (see the review article cited on page 23, line 2 of specification). Similarly, causation of the clearance of CD4(+) T lymphocytes and of other inflammatory cells from lesional skin within a few days of treatment by the present method is highly surprising in view of the effects on said cells and lesions by the prior art treatments directed to said cells.

(x) *Beachy et al* teach that treatment with an antiproliferative embodiment of the subject method will provide sustained remission of the disease in a patient having psoriasis (column 41, lines 54-57). However, a minimal dose of a Hh antagonist effective to cause inhibition of proliferation of the epidermal cells in psoriatic lesional skin clearly fails to cause normalization of lesional skin. Further, it is described in the present application with actual treatments of psoriasis patients that the treatment for a day failed to cause clearance of lesions in about one third of cases and the *lesions showed worsening upon discontinuation of administration of cyclopamine* (see page 27, lines 8-12). This is an outcome unexpected from the teaching of *Beachy et al* stating that causation of an inhibition of proliferation effect in psoriasis will cause sustained remission of the disease.

Fulfillment of the Requirements of 35 USC §103 In view Of the *KSR vs Teleflex* Decision

The Examiner refers to the *KSR v. Teleflex* decision for support of the rejection of instant claims 32, 34, 36. However, the pertaining facts in said decision and in the present case are different and the extrapolation made by the Examiner from said decision to the present case is erroneous and inappropriate. Rather, the basic principles emphasized in the *KSR v. Teleflex* decision show further that the requirements of 35 USC §103 are fulfilled by instant claims.

The US Supreme Court has stated in said decision that "When…there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options". Concerning the *KSR vs Teleflex* case, the Court added that "…a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" and pointed out to earlier decisions finding compliance with 35 USC §103 when the prior art warned against a certain solution or was teaching away.

In addition, in March of 2008 *Ortho-Mcneil Pharmaceutical Inc. v. Mylan Laboratories Inc.* 86 USPQ2D 1196, the Federal Circuit pointed that an inference of obviousness on the basis of this *KSR* statement is improper when the available options provided in the prior art are not a small and finite number of alternatives that can be easily traversed. *Beachy et al* does not present a small, finite number of alternatives which can be easily traversed to come up with the present invention. The Examiner's reasoning in the outstanding rejection is the kind of obviousness argument that has been repudiated in *Ortho-Mcneil.*

Beachy et al disclose an infinite number of compounds for "treatment" of an extremely long and open-ended list of disorders without a single instance of a treatment of an enlisted disorder. The number of possible effects or results to be determined by the skilled artisan (i.e. "solutions") becomes further astronomical or infinite when it is considered that the term "treatment" of a disorder or clinical condition in medical practice may mean causations of very different technical effects and very different therapeutic results.

Nothing in prior art had identified that administration of a Hh antagonist, in a dose that surpasses one that is sufficient to inhibit proliferation of the epidermal cells, will result in induction of differentiation of said cells in lesional skin and produce clearance of the lesions. Furthermore, causation of an *inhibition of differentiation* effect rather than the described induction of differentiation was the naturally predicted effect in prior art. In prior art, Hh signaling was found to be broadly employed for induction of differentiation of various cells, including the epidermal cells. Thus, in terms of the predicted effect, the prior art was teaching away from the subject matter of claims 32, 34 and 36. Likewise, the prior art had concluded on the basis of extensive investigations and decades of treatment results that it is unrealistic to expect full disappearance or clearance of lesions. The unprecedented efficacy of present treatment in causation of clearance of psoriasis lesions was highly unexpected in view of prior art. In addition, the prior art had warned against administering a Hh antagonist to an adult, finding employment of Hh signaling for normal functioning of various cells and an absolute dependence of stem cells on Hh signaling. The presently described sparing of the undifferentiated cells in epidermis basal layer and in hair follicles (well known sites of stem and progenitor cells) and the display of normal hair and skin in the long-term followed up patients at former sites of treatment are objective evidence of an advantageous and unexpected safety. Thus, both the primary considerations and secondary considerations show that claims 32, 34 and 36 describe subject matter unexpected and nonobvious in prior art.

It must also be added that the presently claimed subject matter is not inherently present in a use described in prior art for cyclopamine and a skilled artisan following the teachings of prior art would not be able to obtain the results recited in claims 32, 34 and 36. In prior art, administration of a dose of cyclopamine surpassing what is sufficient to inhibit proliferation of the epidermal cells so as to induce differentiation of the epidermal cells in lesional skin and to produce clearance of lesions was neither a known option nor an expected option.

In conclusion, the presently claimed invention fulfils the requirements of 35 USC § 103 also in consideration of the principles emphasized by the US Supreme Court in the *KSR v. Teleflex* decision and by the Federal Circuit in *Ortho-Mcneil Pharmaceutical Inc. v. Mylan Laboratories Inc.*

Rejection Of Claim 34

Examiner appears mistaken in reading *Beachy et al* in rejecting claim 34 for being obvious in view of *Beachy et al,* column 28, lines 40-55. *Beachy et al* teach rather *away* in column 28, lines 40-55 and elsewhere. In the passages in column 28, line 36 to column 29, line 9 *Beachy et al* teach that a Hh antagonist is to lack a binding specificity or selectivity to a member of the nuclear hormone receptor superfamily and to lack in this manner biological activity and unwanted effects that may arise from corticosteroid administration (see also claims 7 and 8). Well-known dose related effects of corticosteroid administration, e g hyperglycemia, muscle wasting, hypertension, increased susceptibility to infections and Cushinoid features are listed and an antagonist of Hh signaling is said to avoid these (column 28, line 65 to column 29, line 9). The problems of corticosteroid administration explicitly described by *Beachy et al* provide reasons why a skilled person would not have wanted to formulate a corticosteroid in combination with an antagonist of Hh signaling. Thus, *Beachy et al* teach away from the subject matter of claim 34 and said claim is not made *prima facie* obvious by *Beachy et al.*

Subject matter of claim 34 is unexpected and nonobvious in view of *Beachy et al* and the rest of prior art for other reasons as well. The clinical investigation results presented in the specification of application show that administration of cyclopamine in combination with a corticosteroid provides enhanced regression and clearance of psoriatic lesions in comparison to the administration of cyclopamine alone (page 4, lines 18-22; page 25, line 19 to page 27, line 19; Table I) Statistical analyses of the data shown in Table I demonstrate causation of a synergistic effect (i.e. more than an additive increase in therapeutic efficacy) when a corticosteroid is combined with cyclopamine. Table I shows in this respect that even after a single day of treatment (during which time a corticosteroid is well known to have no detectable effect on the severity scores of lesions), administering cyclopamine in combination with a corticosteroid results in significantly increased efficacy over administration of cyclopamine alone. Particularly since an unprecedented therapeutic efficacy was already obtained by administration of cyclopamine alone, a further (and more than additive) improvement in therapeutic efficacy is unexpected. Further, it is well known in art that combination of a pharmaceutical agent effective in treatment of psoriasis or another disorder with a corticosteroid may provide no additional benefit at all, let alone creation of a synergy. The unexpected synergy is sufficient to establish non-obviousness even if *prima facie* case of obviousness was present. MPEP 2145.

Claim 34 is therefore nonobvious in view of *Beachy et al* and the rest of prior art.

III. Conclusion

In view of the foregoing amendment and remarks, the rejections of claims 32, 34 and 36 are seen to be overcome. Accordingly, withdrawal of the rejections and allowance of the application is respectfully requested.

Respectfully submitted,
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